REMARKS

Claims 1 and 3-22 are pending in the subject application. Claims 5, 6, and 14-22 are withdrawn as being directed to a non-elected invention. Claims 2 and 23 are cancelled. Claims 1, 3, 4 and 7-13 are rejected. Applicants have amended claim 1 and respectfully request reconsideration in view of the following remarks. No new matter has been added.

Claim Rejection under U.S.C. § 103(a)

Le Douarin et al. in view of Scanlan et al.

Claims 1, 3, 4, 7 and 9-12 are rejected as being unpatentable over Le Douarin et al. (The EMBO Journal, Vol. 15, No. 23, pages 6701-6715, 1996) in view of Scanlan et al. (U.S. Patent No. 6,236,946). Specifically, the Examiner contends that Le Douarin et al. teach a 10 amino acid sequence in TIF1, i.e., the "NR box", which comprises the sequence LXXLLL. Further the Examiner contends that while Le Douarin fails to disclose the addition of potential inhibitors, Scanlan et al. teach computational methods to design drugs for nuclear receptors, including retinoid (RX) receptors which can be tested using assays to establish activity as an agonist, partial agonist or antagonist.

Claim 1 recites an 8-10 amino acid fragment of a nuclear protein comprising only one signature motif B^1XXLL, in which B^1 is any natural hydrophobic amino acid. Claim 1 has been amended to recite that the 8-10 amino acid fragment of (ii) does not comprise a "NR box" sequence. The "NR box" of Le Douarin et al. referenced on page 1, lines 24-26 of the present application and appearing in Figure 3D, page 6705 of the EMBO article comprises the signature sequence: "LXXLLL" wherein in exemplary embodiments such as in the TIF1 protein the NR box is "ILTSLLLNSS". As amended, the present claims exclude a sequence or signature motif disclosed in Le Douarin and Le Douarin neither teach nor suggest sequences that lack an NR box comprising an LXXLLL motif. Accordingly, the cited references fail to teach or suggest all elements of the claims as amended.

Scanlan et al. disclose computational methods for the design of synthetic ligands which are small molecules that bind to nuclear receptors. Scanlan does not however teach or suggest the use of a liganded nuclear receptor with a nuclear protein fragment or a potential inhibitor, no less sequences comprising the motif B^1XXLL but lacking the NR box sequence LXXLLL. Scanlan, therefore, does not overcome the deficiencies of Le Douarin and the references together fail to teach all components of the present claims.

The signature motif of the present claims is substantially more powerful for identifying potential inhibitors of the liganded nuclear receptor-nuclear protein interaction than the motif disclosed by Le Douarin. For example, the motif of the present claims is conserved in at least 39 sequences as disclosed in the present specification, Figures 3A and 4. Moreover, in certain nuclear proteins, the signature motif appears multiple times in a single nuclear protein which is not the case for the "NR box" of Le Douarin et al. For example, the motif B^1XXLL of the present claim repeats seven times in the protein RIP140, while the "NR box" of Le Douarin et al. appears only once within the sequence. The motif of the present claims therefore is not only conserved in a far greater number of proteins but elucidates how liganded nuclear receptors interact with nuclear proteins as a class because it identifies a plurality of sites picked out by the signature motif of the claimed invention within a single nuclear protein.

Furthermore, the breakthrough provided by the presently claimed invention is evident from the commentary by Marc Montminy (Montminy, Nature (1997), 387, 654-655) presented in the same issue as the subject inventors' publication in the peer-reviewed journal Nature (Heery et al., Nature (1997), 387, 733-736). In particular, Montminy describes how "...characterizing the mechanisms by which nuclear factors engage the transcriptional apparatus in response to hormonal stimulation has seemed, at times, to be an insurmountable task." Montminy follows-up with the statement that the discovery of a short peptide motif as set forth in the Nature publication and the present claims "...has implications for understanding the mechanisms by which nuclear receptors ultimately interact with the transcriptional machinery in a signal-dependent manner." The comment by Montminy that the achievement overcomes an "insurmountable task" is strong objective

evidence of unexpected results (MPEP § 2141 V) and the glowing reception by peer scientists makes clear that this invention was not obvious or predictable from the prior art.

Le Douarin et al. in view of Dedhar

Claims 1, 3, 4, 7 and 9-13 are rejected as being unpatentable over Le Douarin et al. in view of Dedhar (U.S. Patent No. 5,854,202). Specifically, the Examiner asserts that Le Douarin et al. teach a 10 amino acid sequence in TIF1, i.e., the "NR box", which comprises the sequence LXXLLL. The Examiner concedes that Le Douarin fails to disclose the addition of potential inhibitors but that Dedhar teaches that it is desirable to identify peptides that modulate the activity of hormone receptors and determine if they inhibit or promote receptor induced gene transcription. Specifically, the Examiner contends that it would have been obvious to modify the interaction assay of Le Douarin et al. to include the administration of peptides, wherein the peptides are of a conserved sequence and are tested for modulation of nuclear hormone receptor-receptor protein interaction as in Dedhar.

As discussed in detail above, the claims have been amended to exclude the "NR box" of Le Douarin et al. Dedhar discloses the use of a motif "KXFFXR" – entirely unrelated to the motif set forth in the pending claims – derived from the protein calreticulin that is critical for DNA binding activity. Dedhar does not teach a method for identifying an inhibitor compound capable of reducing the interaction between a first and second component comprising placing in contact a potential inhibitor compound, a component comprising the signature motif B^1XXLL and a liganded nuclear receptor. As such, Dedhar fails to overcome the shortcomings of Le Douarin to teach all components of the present claims. Applicants respectfully request reconsideration of the claims as amended.

Le Douarin et al. in view of Dedhar in view of Collingswood et al. in view of Spencer et al.

Claim 8 is rejected as being unpatentable over Le Douarin et al. in view of Dedhar in view of Collingswood et al. and Spencer et al. Applicants traverse in light of the comments made above

regarding Le Douarin et al. and Dedhar and add that Collingswood et al. (PNAS, USA, Vol. 94, pages 248-253, 1997) and Spencer et al. (GenBank Accession No. U90661.1, GI:1906027, 1997) fail to overcome the deficiencies of the former references as discussed in detail above. Reconsideration of the claim is requested.

In view of the above remarks, Applicants believe the pending application is in condition for allowance. If a fee is due with this response, please charge our Deposit Account No. 18-1945, under Order No. ASZD-P01-228 from which the undersigned is authorized to draw.

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Respectfully submitted,

By _____

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